Editorial Comment

Managing Patients Who Have Myasthenia Gravis

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Myasthenia gravis is reported to have an incidence of 1:20,000 to 1:40,000 in the United States. Those estimates are probably low, as mild forms may not come to the attention of a physician, acutely severe cases may lead to sudden death and all forms may present difficulty in diagnosis.

In the past 20 years, the physiologic and immunologic bases of myasthenia gravis have been remarkably elucidated. Even though important questions remain unanswered, the treatment and management of patients have improved so that the 35% mortality of 20 years ago has dropped to almost zero. Deaths are more often due to associated or complicating illnesses. Although many patients require care for respiratory failure, their stay in special care units has been greatly reduced. In some series, 75% to 80% of patients have marked improvement or remission with therapy, so that they are able to return to their jobs or ordinary activities.

While Eaton-Lambert syndrome (facilitating neuromuscular block) and botulinum intoxication are examples of presynaptic (prejunctional) disorders due to impairment of transmitter (acetylcholine) formation or release, myasthenia gravis is largely a postsynaptic (postjunctional) disorder. The number of effective acetylcholine (ACh) receptors is reduced, perhaps because anti-ACh-receptor antibodies cause increased turnover of ACh receptors and a decreased number of sites. It is unlikely that the anti-ACh-receptor antibodies are all of one type. The most common precipitation technique using human ACh receptor as antigen shows antibodies in 75% to 94% of patients. Antibodies against ACh receptor have been produced in human thymus cell cultures. There is no firm relationship between antibody levels and severity of illness in groups of patients, although a single patient may have improvement, such as with plasma exchange, as his or her ACh-receptor antibody levels decrease. Some patients with myasthenia gravis have antibodies to thyroid, gastric parietal cells, bone marrow, ovary or striated muscle (especially with thymoma).

From a pharmacologic standpoint, patients with postsynaptic disorders are treated with cholinesterase inhibitors such as neostigmine and pyridostigmine bromide, and those with presynaptic disorders are treated with calcium gluconate, guanidine (now out of favor because of associated hemolytic anemia) or the aminopyridines (4-AP and 3,4-DAP). The use of cholinesterase inhibitors, the mainstay of therapy for myasthenia gravis from 1934 until only five or six years ago, has been deemphasized in recent reports. Because cholinesterase inhibitors represent only symptomatic therapy, they are of little aid in most cases of moderate to severe or of progressive myasthenia gravis, particularly if there is oropharyngeal or respiratory muscle involvement.

In the UCLA conference on myasthenia gravis in this issue, much of the great wealth of knowledge of this disorder is reviewed. Physicians who manage patients with myasthenia gravis must have the neurologic acumen to consider the problems of differential diagnosis, which are largely a function of which skeletal muscles are first involved: a recent onset of weakness of unilateral medial and superior rectus and levator palpebral muscles; progressive proximal pectoral or pelvic girdle weakness (or both); subacute or slowly progressive oropharyngeal muscle weakness with dysphonia, dysphagia or dysarthria, or bilateral medial or lateral rectus weakness. The foregoing refer to the following differential considerations, in the same order: oculomotor nerve disease, as with diabetes mellitus or a posterior communicating artery aneurysm; myopathy, such as polymyositis or, with more rapid evolution, an acute inflammatory demyelinating polyneuritis (Landry-Guillain-Barré syndrome); amyotrophic lateral sclerosis or glioma of the medulla, and internuclear ophthalmoplegia with involvement of the paramedian pontine tegmentum by an infarct or a plaque of multiple sclerosis.

Physicians assuming responsibility for the management of patients with myasthenia gravis must understand the pathogenesis of the illness, including the major and recent advances in physiology, pharmacology and immunology. In many instances we assume the responsibility of the critical care of patients with respiratory failure and the care of patients before and after thymectomy. Furthermore, we are responsible for evaluating the course of the illness and response to therapy both over the short term of hours (cholinesterase inhibitors and plasma exchange) or the longer term of days, months and even years (corticosteroids, antimetabolites, plasma exchange and thymectomy). Regardless of the outcome of therapy that modifies immune mechanisms, we assume responsibility for following such patients for 15 to 20 years, or perhaps to the end of their lives.

Although corticosteroids have been reported to be of value

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in cases of myasthenia gravis for almost 15 years, they have been generally accepted for only 5 years. The data suffer from being uncontrolled retrospective series using various dosage regimens and poorly standardized assessment methods. However, the data available do provide physicians and patients with guidelines and expectations with optimal use of those drugs.

University of Virginia Experience

We have recently reviewed our experience at the University of Virginia with long-term administration of corticosteroids in the management of 116 consecutive patients with disabling or life-threatening myasthenia gravis.[1] Patients received cholinesterase inhibitors early in the course of treatment, if they were of benefit. Neither antimetabolites nor plasma exchange were administered during the period when prednisone effectiveness was being determined. A total of 41 male and 75 female patients aged 8 to 82 years were treated with a regimen of high-dose daily prednisone, 60 to 80 mg per day. Following the *onset* of improvement, the regimen was changed to an equivalent alternate-day dosage (120 to 160 mg), with gradual reduction at a rate of about 10 mg every six to ten weeks, provided the improvement continued toward the goal of marked improvement or remission. Thereafter, reductions of dosage were permitted only if satisfactory improvement was maintained. Overall, the results were favorable in 80.2%, with remission in 27.6% and marked improvement in 52.6%, while 14.7% showed only moderate improvement with significant residual symptoms and 5.2% did not have improvement. Exacerbation early in treatment occurred in 48% of patients, but was severe in only 8.6%, with the onset between day 1 and day 17, and with a mean duration of 4.2 days. The risk of early exacerbation required initiating high-dose prednisone therapy on an inpatient basis. Improvement began after a mean of 13.2 days of therapy, ranging from 12 hours to 60 days. Nine patients (7.8%) did not have the onset of sustained improvement until after 30 days of treatment. In patients with severe disease, or for those who have tolerated prednisone therapy for 30 days with no complications, one should consider maintaining therapy for up to 60 days before concluding that a patient will not respond.

The improvement was gradual, with *maximal* improvement occurring at a mean of 9.4 months. An equally important observation was the period to achieve *marked* improvement, which occurred at a mean of 3.1 months. Of those patients with a satisfactory response, most maintained their improvement with gradual dosage reduction. In all, 14% were able to discontinue prednisone therapy completely, while 18% required a minimal dose (5 to 50 mg on alternate days) to maintain their improvement. Thymectomy was done in many patients following their achieving maximal or marked improvement, but thymectomy was not a factor in determining which patients were able to discontinue prednisone therapy. Of patients achieving a satisfactory response, 18% later had one or more slowly evolving but significant exacerbations, most often related to a too-rapid reduction in dosage. The more common side effects of prednisone therapy, cushingoid appearance (33%) and weight gain (18%), were dose and duration dependent and resolved in large part when the regimen was changed to alternate day and the dosage reduced. Other complications included cataracts (26%), diabetes mellitus (12%), hypertension (12%), osteoporosis (9%), compression fracture (5%), aseptic necrosis of the hip (4%) and a lower incidence of infection, psychological disturbance, gastrointestinal complications and glaucoma. They occurred with ill-advised high-dose treatment for a longer duration or in patients whose first course of treatment was unsatisfactory in either magnitude or duration, and was followed by a second and sometimes a third course of therapy. The likelihood of cataracts was discussed with patients before instituting therapy, and it was generally agreed to be an acceptable complication.

Multivariate analysis showed that patient age was the greatest factor in the response to therapy, with older patients having a greater likelihood of a favorable response. Sex, classification of disease, disease duration and the presence of thymoma were *not* significant factors in the response to prednisone therapy. Our finding that patients with myasthenia gravis and thymoma responded favorably to prednisone therapy is quite contrary to previous published reports. Sghirlanzoni and co-workers in Milan have recently published similar results in 60 patients.[2] Therefore, the physician has data with which to predict the likelihood and time course of response to prednisone therapy and the long-term expectations and possible complications.

Discussion

Considering the preceding data and that from the UCLA conference, how does a physician choose between cholinesterase inhibitors, plasma exchange, corticosteroids, antimetabolites and thymectomy?

One must consider, first, the natural course of the illness. Perhaps 50% of patients with myasthenia gravis present with ocular involvement, but about 80% may have ocular involvement after one month. If there is only ocular involvement after one year, it is likely that the disease will remain mainly ocular. Spontaneous remissions of more than one or two years' duration probably occur in less than 10% of patients, and they tend to be in persons with mild or localized muscle weakness. Simpson has proposed classifying three stages of myasthenia gravis: active stage—increasing severity of weakness with a fluctuating course (most labile, usually lasting five to ten years); inactive stage—less fluctuation (less labile, follows the initial five to ten years), and burned-out stage—relative absence of fluctuation, frequent permanent weakness or atrophy (occurs 14 to 20 years after onset of symptoms).[3] Although one can debate Simpson's proposal, it has merit in characterizing the illness of many patients. (Our own experience has been that patients with myasthenia gravis of more than ten years' duration, including some with atrophy, do respond to prednisone therapy.) Often, a physician may not wish to treat a patient with ocular myasthenia gravis with immunosuppression. In some cases, however, ocular impairment may cause great disability (such as in a dentist or a bus driver) and merit the use of prednisone or azathioprine.

One should compare the therapeutic modalities as follows: the time until onset of improvement following institution of therapy; the time until maximal improvement occurs; the outcome, in terms of likelihood of achieving marked improvement or remission; the duration of maintenance of improvement; the untoward side effects, and the financial costs.

Cholinesterase inhibitors alone may be of value in cases of ocular or mild limb involvement that is essentially not progressive. The onset and duration of action is in terms of hours.

Plasma exchange will lead to marked improvement or remission in about 45% of cases, with the improvement beginning between the first to the fourth exchange and maximal improvement occurring from the first to the 15th exchange (with a regimen of three exchanges a week). However, improvement is for only 4 days to 12 weeks. Some patients who have been pretreated with prednisone or azathioprine have sustained improvement for longer periods. Obviously, plasma exchange may be used on an urgent basis in a myasthenic crisis with respiratory distress, often obviating the prolonged use of an airway or respirator. Plasma exchange may be used as an adjuvant form of therapy, following corticosteroids or antimetabolites or concurrent with them. The recent reports of good intermediate-term results with only plasma exchange followed by thymectomy have not, as of now, been adequately documented.

Corticosteroids will lead to marked improvement or remission in about 80% of cases, with improvement beginning from between 12 hours and 30 days (mean, 13 days) and marked improvement occurring in from 1½ weeks to 18 months (mean, 3 months). Improvement is maintained even with decreasing dosage on an alternate-day regimen. About 14% have maintained improvement after discontinuation of therapy.

The antimetabolite azathioprine is difficult to evaluate because it has often been used along with corticosteroids and thymectomy. One series in the United States indicated that about 45% had some degree of improvement using azathioprine alone.[4] Improvement begins at from 3 to 12 months, and maximal improvement occurs in from 12 to 36 months. Improvement is maintained only when the high initial doses are maintained: about 10% of patients may have maintained improvement after discontinuance of therapy. Mertens and associates and Matell report a "remission" rate of 40%, but these data are flawed by the concurrent use of corticosteroids.[5,6] It must also be emphasized that the German and Swedish experiences with azathioprine have not included favorable results with cases of acute, severe myasthenia gravis. The use of cyclophosphamide in some small series has led to improvement in 74% of patients, with an earlier response. All those studies are retrospective and uncontrolled.

Thymectomy may lead to some degree of improvement in about 76% of cases and to remission in about 35%, with improvement occurring over a few months to more than ten years. One report indicates that of those who achieve remission, 50% will have achieved it in 2½ years, while 25% will *not* achieve it for 5 to 10 or more years.[7] The UCLA conference presents data to indicate that the best results were in patients with "more mild" disease.

The value of thymectomy remains an enigma, since the effectiveness must be evaluated over two to ten or more years. The lure of early improvement, from hours to months after surgical procedure, has yet to be substantiated. Nevertheless, observing the most favorable results and the improvements in surgical technique, anesthesia and respiratory management that have led to almost zero mortality, thymectomy for myasthenia gravis has become increasingly recommended. We urge thymectomy as soon as possible in patients in excellent condition (often having been treated with prednisone beforehand) to minimize operative morbidity. There appear to be no truly reliable criteria for determining which patient will respond to thymectomy in spite of the opinions generated 25 to 45 years ago that young women with illness of short duration had the best prognosis. The criteria to determine whether thymectomy is indicated should be precise, but are not. Most consider the indication to be progressive or severe generalized myasthenia, and a few groups believe that young patients with new disease are the only proper candidates. It seems to me that, if thymectomy *is* appropriate treatment for myasthenia gravis, all patients in whom the diagnosis is firmly established should have their thymuses removed. That conviction arises from our experience that spontaneous remissions that persist are uncommon and from the knowledge that from 10% to 20% of patients with myasthenia gravis will have thymomas. Furthermore, once patients have myasthenia gravis, thymoma may develop at any time in the course of their illness. Thus, one must not have concern for thymoma only at the beginning of the illness.

Obviously there are contraindications to thymectomy, as there are for any major operative procedure on the thorax. Also, because the favorable results from thymectomy appear to accrue over 5 to 10 years or more, one must expect longevity of 10 to 15 years or more.

Thymectomy before adolescence is of more concern, partly because of the threat to growth rate. We have preferred to administer corticosteroids, monitor growth and delay thymectomy until the immediate postpubertal period or later.

There is controversy over whether patients should be treated with corticosteroids before thymectomy, or vice versa. Scientifically, there is no doubt that using both therapeutic methods in the same time frame impairs the evaluation of long-term results of therapy by either modality alone. We have treated patients with corticosteroids first because the predictable response is much more rapid than the response to thymectomy; most of our patients have had moderate to severe myasthenia with oropharyngeal weakness, and otherwise management in the perioperative period would be fraught with complications and result in a prolonged stay in the intensive care unit.

It is apparent that corticosteroids are preferable to antimetabolites when one considers the rapid onset of improvement and the earlier achievement of marked improvement. That is particularly the case in patients with acute severe myasthenia gravis with respiratory failure, dysphagia or both. Only if a physician adheres to a regimen of prednisone that avoids other than transient untoward side effects can one justify the use of corticosteroids—with their earlier favorable results. We found the most effective regimen, with the highest therapeutic index, has been high-dose daily prednisone, proceeding to an alternate-day regimen at the time of a definite onset of improvement, then gradual reduction of dose to maintenance, only with the patient continuing to improve, or having achieved marked improvement or remission. In less acute cases, the use of azathioprine is effective, with the later onset of improvement and later achievement of marked improvement. In these cases, the hematologic and hepatic side effects of azathioprine become a major consideration, partly because of the increased risk of infection.

Although most patients are effectively managed with one

or more of the above therapeutic modes, perhaps 10% respond poorly. Also, each mode has morbidity, though of debatable magnitude. There is clearly a need for the development of more effective therapy with less morbidity. We must proceed to combination therapy involving immunosuppressive drugs, plasma exchange and thymectomy.

The following major questions remain regarding the nature of myasthenia gravis:

- What initiates the production of antibodies to acetylcholine receptor? Is it an inflammatory process in the thymus, or perhaps a viral infection altering cell surface membranes and making the cells antigenic?
- How do anti-ACh-receptor antibodies produce neuromuscular blockade? The antibodies react with sites adjacent to the ACh-binding site (the α-bungarotoxin-binding site). They may lead to turnover or destruction of the adjacent ACh receptor, or they may physically interfere with the reaction of ACh and its receptor. It seems unlikely that the antibodies directly block cationic channels. Lindstrom has dealt with that issue superbly in this UCLA conference.
- Why are some muscles involved and others spared? It appears that the efficiency of neuromuscular transmission (safety margin), which may vary from one muscle group to another in animals, is not the entire explanation, since involvement is often asymmetric and muscles uninvolved in one period of illness may be involved in a later period. Why are there remissions and exacerbations?
- What is the role of the thymus and, if thymectomy is helpful, why is improvement delayed for many months to ten years? Does the thymus produce the antibody, the antigen or both? Is delay of response due to long-term circulating lymphocytes?
- Which patients are most likely to respond to a particular treatment modality?
- Is plasma exchange effective because it removes anti-ACh antibodies, or something else?
- Are there geographic or environmental factors operating in the incidence of myasthenia gravis?

At our present state of knowledge, every patient with myasthenia gravis should be reviewed by a physician with expertise in differential diagnosis and in the use of pharmacologic and immunosuppressive therapy. Review should continue at regular intervals during the use of major therapeutic agents.

We must evaluate the effectiveness of other immunosuppressive agents such as cyclophosphamide and methotrexate in prospective controlled studies. The use of cyclosporin—which may act to suppress selectively aberrant antibody production—the development of anti-idiotype antibodies and the use of pooled γ-globulin may provide insight into immune regulation in patients with myasthenia gravis.

It is likely that the experts will have varying opinions regarding the specific indications for treatment and the choice of therapy. Nevertheless, all of us, whether in private or institutional practice, have an obligation to participate in controlled prospective therapeutic trials. It seems quite unlikely that the management of patients who have myasthenia gravis will improve further without dedicated participation by each of us.

Tremendous progress has been made in the understanding and management of myasthenia gravis. Scientific advances have had a great impact, but so have serendipity and empiricism. With further research, with better keeping of records and with controlled studies of some modes of therapy, the above questions will be answered.

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